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Complete List of Authors:	Schijvens, A; Radboudumc, Pediatric Nephrology Dorresteijn, E; Erasmus MC Sophia, Pediatric Nephrology Roeleveld, C; Radboudumc, Health Evidence ter Heine, R; Radboudumc, Pharmacy van Wijk, J; VU medisch centrum, Pediatric Nephrology Bouts, A; AMC, Pediatric Nephrology Keijzer - Veen, M; Universitair Medisch Centrum Utrecht, Pediatric Nephrology van de Kar, N; Radboudumc, Pediatric Nephrology van den Heuvel, L; Radboudumc, Pediatric Nephrology; Universitaire Ziekenhuizen Leuven, Growth and Regeneration Schreuder, Michiel; Radboudumc, Pediatric Nephrology
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REducing STEroids in Relapsing Nephrotic syndrome: the RESTERN study – protocol of a national, double-blind, randomised, placebo controlled, noninferiority intervention study

Schijvens AM[1], Dorresteijn EM[2], Roeleveld CJA[3], ter Heine R[4], van Wijk JAE[5], Bouts AHM[6], Keijzer-Veen MG[7], van de Kar NCAJ[1], van den Heuvel LPWJ[1,8], Schreuder MF[1]

[1]Department of Pediatric Nephrology, Radboudumc Amalia Children's Hospital, Nijmegen, The Netherlands;
[2]Department of Pediatric Nephrology, Erasmus MC - Sophia Children's Hospital, Rotterdam, The Netherlands;
[3]Department for Health Evidence, Radboudumc, Nijmegen, The Netherlands;
[4]Department of Pharmacy, Radboudumc, Nijmegen, The Netherlands;
[5]Department of Pediatric Nephrology, VU University Medical Center, Amsterdam, The Netherlands;
[6]Department of Pediatric Nephrology, Academic Medical Center, Amsterdam, The Netherlands;
[7]Department of Pediatric Nephrology, University Medical Centre Utrecht, Utrecht, The Netherlands;
[8]Department of Pediatrics, Department of Growth and Regeneration, University Hospital Leuven, Leuven, Belgium.

Corresponding author:
Anne Merel Schijvens, MD
Department of Pediatric Nephrology
Radboudumc Amalia Children's Hospital
P.O. Box 9101, 6500 HB Nijmegen
The Netherlands, +31 24 36 16783
Anne.Schijvens@radboudumc.nl

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ABSTRACT

Introduction

Oral corticosteroids are the first-line treatment for idiopathic childhood nephrotic syndrome. Most children experience several relapses, needing repeated courses of corticosteroid therapy. This exposes them to side-effects and long-term complications. For most patients, long-term prognosis is for complete resolution of the disease over time and maintenance of normal kidney function. Therefore, it is vital to focus on minimizing adverse events of the disease and its therapy. Unfortunately, no randomised controlled trials are available to determine the optimal corticosteroid treatment of an infrequent relapse of nephrotic syndrome. Recent studies show that treatment schedules for the first episode can safely be shortened to two months. The hypothesis of the RESTERN study is that a 4-week reduction of alternate day steroids after inducing remission is effective and safe, reduces steroid exposure by 35% on average, and is therefore preferable.

Methods and analysis

The RESTERN study is a nation-wide, double-blind, randomised, placebo controlled, noninferiority intervention study. Children aged 1-18 years with a relapse of steroid sensitive nephrotic syndrome are eligible for this study. Study subjects (n=144) will be randomly assigned to either current standard therapy in the Netherlands or a reduced prednisolone schedule. The primary endpoint of the RESTERN study is the time to first relapse after the final prednisolone dose. The secondary endpoints are the number or relapses, progression to frequent relapsing or steroid dependent nephrotic syndrome and the cumulative dosage of prednisolone during the study period.

Ethics and communication

This noninferiority trial will be performed in accordance with the Declaration of Helsinki and has been approved by the medical ethical committee of Arnhem-Nijmegen and the Dutch Competent Authority (Central Committee on Research Involving Human Subjects, CCMO)

Registration details

Trial registration number NTR5670, EudraCT number 2016-002430-76.

Keywords

Nephrotic syndrome, pediatrics, corticosteroids, randomised clinical trial

Strengths and limitations of this study

- Double-blind, randomised, placebo controlled study
- Nation-wide inclusion
- Large study cohort
- Two common practices in the Netherlands regarding the current treatment of relapsing nephrotic syndrome

INTRODUCTION

Nephrotic syndrome is characterized by the triad of severe proteinuria, hypoalbuminaemia and edema. It is one of the most common glomerular diseases in children with an incidence of 1-7 per 100,000 children per year (Dutch data: 1.52/100,000) and a prevalence of 16 per 100,000 children.[1-3] Most children have minimal change nephrotic syndrome and will have favorable prognosis with complete resolution of the disease over time and maintenance of normal kidney function.[4]

For over 60 years corticosteroids have been the first-line treatment for idiopathic nephrotic syndrome in children as over 80-90% of patients achieve complete remission after prednisolone treatment.[5,6] Yet, over 80% of the patients experience one or more relapses and around 50% suffer from frequent relapses, thereby needing additional courses of corticosteroid therapy.[7] This exposes them to the side effects and long-term complications of corticosteroid therapy, such as growth retardation (8-16%), osteopenia (13-63%), mood disorders, and cataract (6-20%).[8-11] The currently used treatment regimens for a nephrotic syndrome relapse are mostly based on practice guidelines of the International Study of Kidney Disease in Children (ISKDC)[12] and the Arbeitsgemeinschaft für Pädiatrische Nephrologie (APN)[13]. In the Netherlands, the standard treatment schedule consists of 60

mg/m^2 prednisolone daily until complete remission is achieved for 3 days, followed by 40 mg/m^2 prednisolone on alternate days for 4-6 weeks.[14,15]

Several trials have been conducted to study the duration of the initial corticosteroid treatment regimen, as Hodson et al. suggested that a prolonged period of prednisolone might reduce chances of subsequent relapses.[16] A previous nation-wide study in the Netherlands addressed the issue of duration of corticosteroids for the initial presentation, and showed that the duration had no impact on subsequent relapses.[7] A few recent, well-conducted trials suggest that it may be safe to reduce the duration and thereby cumulative dose of corticosteroid therapy for the initial episode of nephrotic syndrome from six to two or three months.[17-21] With recent studies showing no benefit for longer duration of initial prednisolone treatment, one may conclude that we still don't know the optimal treatment duration of relapses. In addition, as stated in the KDIGO clinical practice guideline glomerulonephritis, "there are no RCTs examining relapse regimens with corticosteroids in infrequent relapsing nephrotic syndrome".[22] With the current evidence against longer steroid therapy for the initial treatment, the time is now to determine whether this holds true for treatment of relapses as well in both children with and without maintenance immunosuppressive therapy.

The aim of the RESTERN study (REducing STEroids in Relapsing Nephrotic syndrome) is to assess the safety and effectiveness of a reduced alternate day steroid schedule for treatment of a nephrotic syndrome relapse in comparison with the current standard therapy.

METHODS AND ANALYSIS

Trial design and setting

The RESTERN study is designed as a nation-wide, double-blind, randomised, placebo controlled, noninferiority intervention study with two treatment arms. The study is performed and coordinated by a single center (Radboudumc Amalia Children's Hospital) where the research team is instituted, with inclusion of patients throughout the Netherlands from all secondary and tertiary hospitals.

Eligibility criteria

Children aged over 1 and less than 18 years with steroid sensitive nephrotic syndrome will be assessed for possible inclusion in the study. A detailed description of the in- and exclusion criteria is shown in Table 1.

Table 1: In- and exclusion criteria

Inclusion criteria
• Age over 1 and less than 18 years
• Steroid sensitive nephrotic syndrome
• At least one episode of nephrotic syndrome in the preceding 24 months that was treated with prednisolone
• The last prednisolone use (at a dose over 10 mg/m^2 on alternate days) for the treatment of a previous episode was at least 4 weeks ago
• Subjects without maintenance immunosuppressive therapy • Subjects with maintenance immunosuppressive therapy ▪ Long term immunosuppressive therapies: levamisole, ciclosporine, tacrolimus, mycophenolate mofetil (Cellcept®), mycophenolate sodium (Myfortic®), prednisolone max. 4 mg/m^2 on alternate days ▪ Cyclophosphamide (oral of intravenous), at least three months post completion of therapy ▪ A single dose or course of intravenous rituximab, at least three months post completion of therapy
• Signed informed consent from the parent or legal representative and/or the patient, depending on the age of the patient

Exclusion criteria
• Steroid resistant nephrotic syndrome
• Receiving, or within 3 months after receiving, cyclophosphamide or rituximab
• Daily prednisolone maintenance therapy at any dose
• Alternate day prednisolone maintenance therapy at a dose over 4 mg/m^2
• Documented or suspected significant non-compliance
• Pregnancy
• Stimulant drug use
• Comorbidity - Kidney transplant recipient - Any disease that requires the variation in oral prednisolone to be at the discretion of the treating physician(s)
• Concomitant use of moderate and strong CYP3A inducers
• Concomitant use of moderate and strong CYP3A inhibitors, other than cyclosporine

Study objectives

The primary objective of this study is to investigate the effectiveness of a reduced steroid schedule for the treatment of a relapse in children with steroid sensitive nephrotic syndrome. Secondary objectives are:

- To study the influence of maintenance immunosuppressive therapy on the effectiveness of a reduced steroid schedule for the treatment of a relapse in children with steroid sensitive nephrotic syndrome. Maintenance immunosuppressive therapies include levamisole, cyclosporine, tacrolimus, mycophenolate mofetil and mycophenolate sodium, and alternate day prednisolone with a maximum of 4 mg/m^2;

- To investigate the occurrence of relapses, frequency of relapses and progression to steroid dependent and frequent relapsing nephrotic syndrome in children with nephrotic syndrome under the standard treatment regimen;

- To study the influence of maintenance immunosuppressive therapy on the occurrence of subsequent relapses, frequency of subsequent relapses and progression to steroid dependent and frequent relapsing nephrotic syndrome under the standard regimen, and;

- To study the effectiveness of a reduced steroid schedule for the treatment of a relapse and

occurrence and frequency of subsequent relapses in children with steroid dependent nephrotic syndrome.

Interventions

Eligible patients will be randomised between standard prednisolone treatment and a reduced treatment schedule. At the start of a relapse, participants are treated according to the current standard therapy, consisting of daily oral prednisolone (60 mg/m^2). After three days of remission, defined as three consecutive days of absent proteinuria based on urine dipstick analysis, standard care dictates that prednisolone is changed to an alternate day dosing of 40 mg/m^2 with a maximum of 40 mg. After two weeks of alternate day prednisolone, participants are randomised between the two treatment arms. The standard treatment group will receive an additional 4 weeks of alternate day oral prednisolone (40 mg/m^2, with a maximum of 40 mg) and the placebo group will receive 4 weeks of alternate day oral placebo.(Figure 1) Prednisolone (5 mg/ml) or placebo will be provided as an oral solution (see paragraph “Investigational medicinal product”).

Children will be withdrawn if they are unable to take the study medication and will be treated according to the standard treatment regimen (oral prednisolone 40 mg/m^2 on alternate days). Maintenance immunosuppressive therapy, including levamisole, cyclosporine, tacrolimus, mycophenolate mofetil and mycophenolate sodium, is continued throughout the treatment period. Alternate day prednisolone maintenance therapy with a maximum of 4 mg/m^2, is discontinued during the non-randomised treatment and restarted after randomisation, administered at the same day as the study medication. Antihypertensive agents, antiproteinuric agents, and/or diuretics may be continued at the discretion of the treating physician.

All children will be followed for two years and subsequent nephrotic syndrome relapses will be treated according to the current standard treatment protocol in the Netherlands.

Investigational medicinal product

A prednisolone or placebo solution (5 mg/ml) will be produced compliant with current Good Manufacturing Practice (cGMP) at the department of pharmacy of our institute. The standardized formulation of the oral solution is based on the Dutch Pharmacists Formulary (FNA). The investigational medicinal product is an aqueous solution preserved with methylparaben, buffered at a pH of 7.1 with a phosphate buffer and contains sorbitol and banana essence to mask the bitter taste of prednisolone sodiumphosphate. For the placebo, prednisolone sodiumphosphate is left out of the product. A pilot palatability study of the investigational medicinal product showed no relevant visual or taste differences of the drug or placebo. Drug dispensing and accountability is performed on individual basis from the central pharmacy.

Outcomes

The primary outcome of the RESTERN study is the time to first relapse. This is defined as the time (in days) from the final prednisolone dose until the first day of treatment of the next relapse.

Secondary outcomes include the following:

1. The number of relapses per patient after the final prednisolone dose, censored at 12 and 24 months of follow-up;

2. Progression to frequent relapsing nephrotic syndrome, defined as four or more relapses in

any 12-month period (KDIGO criteria), censored at 24 months of follow-up;

3. Progression to steroid dependent nephrotic syndrome, defined as two consecutive relapses during corticosteroid therapy, or within 14 days of ceasing therapy (KDIGO criteria), censored at 24 months of follow-up;

4. Cumulative dosage of prednisolone (mg/m^2) during study period, censored at 12 and 24 months of follow-up.

Participant timeline (Figure 1)

During the period of daily prednisolone, participants determine the timing of remission by urine dipstick analysis at least every other day. In order to objectively establish remission of nephrotic syndrome, participants are requested to deliver a urine sample to the local hospital within 5 days of attaining remission to confirm the absence of proteinuria. During the two weeks of alternate day prednisolone and the subsequent 4 weeks of study medication, participants are requested to check their urine for proteinuria at least weekly. In addition, patients are requested to fill out digital questionnaires at different time points. (Figure 1) As shown in Table 2, follow-up information will be collected at 1 and 2 years after randomisation and when a relapse occurs.

Table 2: Study questionnaires

Questionnaire	Information	Time points
Questionnaire 1	General information, medical history, relapse information	At the start of alternate day prednisolone
Questionnaire 2	Information study medication period	One week after initiation of study medication
Questionnaire 3	Information after study medication period	After the final dose of study medication
Questionnaire 4	Information subsequent relapses	At the time of a new relapse

Questionnaire 5	Follow-up 1 year	One year after randomisation
Questionnaire 6	Follow-up 2 years	Two years after randomisation

Sample size

The sample size calculation is based on the noninferiority design and calculated for the primary outcome: time to first relapse after the final prednisolone dose. Based on previous data, average time to relapse in the first year is approximately 185 days with a standard deviation of 120 days.[7] Using the power calculation for a noninferiority trial with a continuous primary outcome, a power of 80% and a noninferiority limit of 50 days, 72 patients per group are required. Using a Cox Proportional Hazard time-to-relapse analysis (survival analysis), similar numbers can be calculated. With an estimated prevalence of nephrotic syndrome of 15 in every 100,000 children, a population most at risk between the ages of 2 and 12 years, about 270 children may be at risk of developing a nephrotic syndrome relapse each year. The necessary inclusion rate is therefore approximately 50%.

Recruitment

Study subjects will be notified about the existence of the RESTERN study via their treating physician, the patient associations and/or the study website (www.restern.nl). Written informed consent for participation will be obtained from the parents or legal representative(s) and/or the patient, depending on the age of the patient.

Randomisation and blinding

Participants will be randomly allocated in a 1:1 ratio to receive either prednisolone or placebo. The randomisation will be performed by the pharmacy of our institute using the data management system Castor Electronic Data Capture[23] with stratification for

treatment with immunosuppressive maintenance therapy. Castor uses a variable block algorithm with random blocks of 4, 6 or 8. The randomisation list remains preserved by the pharmacy and will not be accessible to the investigators until the end of the follow-up of the last patient. An unblinding procedure at the hospital pharmacy department will be available at all times. The true group allocation will be unmasked only if necessary and after the database is locked.

Data collection

Participants are requested to maintain a digital study log in which results from dipstick analysis, medication and special remarks are gathered. In addition, participants receive digital questionnaires about their medical history, previous relapses and side-effects. Local pediatricians and pediatric nephrologists will be requested to provide patient information at different time points. Patients randomised who did not take their allocated treatment will be considered as having deviated from the protocol. If a patient or their representative withdraws consent for data collection, only data up to the point of withdrawal will be used in the analysis.

Data management

The study will use the Good Clinical Practice (GCP) compliant, web-based application Castor Electronic Data Capture to record data.[23] Data will be entered in the case report form in Castor by the coordinating investigators at the Radboudumc. The digital questionnaires will automatically be uploaded in the data management system.

Statistical analysis

Statistical analysis will be conducted using IBM SPSS Statistics. A p-value <0.05 will be considered statistically significant. The main analysis will consist of an intention-to-treat analysis. Participants who are lost to follow-up or in whom trial medication is stopped prematurely will be analyzed according to their allocated groups. In addition, as intention-to-treat analysis may increase the risk of type 1 errors in a non-inferiority trial, a per-protocol analysis will also be conducted.[24] Missing baseline and outcome data will not be imputed. When a patient is lost to follow-up or has withdrawn consent, all available data up until withdrawal of consent or loss to follow-up will be used. Discrete variables will be summarized by frequencies and percentages. Continuously distributed variables will be summarized using either mean and standard deviation (SD) for data with normal distribution, or median and interquartile range (IQR) for non-normally distributed data. Further details regarding statistical analysis of the primary and secondary outcomes can be found in the statistical analysis plan.

Monitoring

As the standard treatment group will receive the current standard therapy for a nephrotic syndrome relapse in the Netherlands, no specific safety surveillance is needed for this group. The placebo arm provides the participants with a reduced prednisolone exposure, which is therefore unlikely to result in any adverse events. However, the main concern in this study is that the reduced treatment schedule may result in an earlier relapse, which is the primary endpoint of the study. An external Data Safety and Monitoring Board (DSMB) will be convened to monitor safety outcomes and to provide the principal investigator with

recommendations regarding reconsideration of the trial. The DSMB will consist of two members: a methodologist and a pediatric nephrologist with experience in clinical trials, both independent of the trial. Interim analysis performed by the DSMB, will take place three months after the first 40 participants have received study medication. Aim is to check for a significant difference in relapse rate between the two groups. Further details about the interim analysis can be found in the statistical analysis plan. An independent research coordinator will monitor the study to verify that the rights and well-being of human subjects are protected, the reported trial data are accurate, complete, and verifiable from source documents and the conduct of the trial is in compliance with the currently approved protocol and GCP. The coordinating investigators will report the serious adverse events and will submit an annual safety report to the medical ethical committee and Competent Authority.

ETHICS AND DISSEMINATION

Ethics approval

The RESTERN study has been approved by the medical ethical committee of Arnhem-Nijmegen and the Dutch Competent Authority (Central Committee on Research Involving Human Subjects, CCMO). The registration number of the RESTERN study is NL8185.091.16. The project will be conducted in line with the declaration of Helsinki. In addition, all researchers will follow the guidelines for Good Clinical Practice and trial outcomes will be reported in line with the Consolidated Standards of Reporting Trials (CONSORT) guidelines.[25] Any substantial amendments or modifications of the protocol will be presented to the medical ethical committee and, when approved, be notified to the Competent Authority compliant with EU regulations.

Consent

Written informed consent for participation will be obtained from the parents or legal representatives and/or the patient, depending on the age of the patient. Patients will be informed that withdrawal from the study is possible at any time at their own discretion without necessarily giving reasons. The 'Code of conduct involving minors' will be used as guideline to respond appropriately to resistance of subjects to study procedures as established by the Paediatric Association Of The Netherlands.

Confidentiality

All patients have their own unique patient identification number as allocated by the hospital administration. Source data will be stored confidentially in the hospital information system under the subject's identification number. Participants will also receive an identification code, all final study data will be kept under this identification number. The investigators safeguard the key to the code. Handling of personal data will comply with the Dutch Personal Data Protection Act. Data will be stored until fifteen years after publication.

Dissemination policy

The trial is registered on the Dutch Trial Registry, trial number NTR5670, prior to the start of inclusion.[26] After completion of this study, results will be published in national and international peer-reviewed scientific journals. Papers will be published according to CCMO guidelines. The final report will be made available to trial participants.

DISCUSSION

The RESTERN study aims to demonstrate that relapses of nephrotic syndrome in children can be treated effectively and safely by a reduced duration of alternate day prednisolone. Using a nation wide, double-blind, randomised, placebo controlled, noninferiority study, the hypothesis will be tested.

Currently, corticosteroid treatment duration in children with infrequent relapses of steroid sensitive nephrotic syndrome is based on empirical recommendations from the ISKDC and APN. The RESTERN study is the first randomised placebo controlled clinical trial to investigate a reduced corticosteroid schedule for the treatment of relapsing nephrotic syndrome in childhood. So far, most studies have been conducted to investigate the initial treatment schedule. Recently, it has been shown that a reduction in prednisolone duration for the treatment of a first presentation of nephrotic syndrome in children, with or without increased cumulative dosage, is clinically safe and results in similar treatment outcomes, while potentially reducing side effects.[17,18,20,21] For frequent relapsing nephrotic syndrome an abstract from a single randomised controlled trial suggests that children with relapsing steroid sensitive nephrotic syndrome relapse less frequently if treated with tapering doses of prednisolone for seven months compared to the standard treatment of two months. Unfortunately, these results have never been published, which makes it impossible to examine them closely and evaluate for any bias.[18,27]

In this study a treatment duration of 6 weeks alternate day prednisolone after inducing remission for the standard therapy group was chosen as this is the current standard therapy in the Netherlands for the treatment of a nephrotic syndrome relapse. However, a potential limitation of this study could be that some clinicians already reduced the alternate day treatment schedule from 6 to 4 weeks after inducing remission based on the notion of this in the KDIGO guideline.[22] Our choice of 6 weeks alternate day prednisolone may therefore discourage eligible patients to participate in our study as this may increase the prednisolone duration for some patients. The use of different treatment protocols in the Netherlands underlines the need for our randomised controlled

trial to determine the optimal dosing regimen for a nephrotic syndrome relapse.

The results of the RESTERN study may provide evidence to adapt current recommendations for national and possibly international guidelines to treat children with relapsing nephrotic syndrome. If corticosteroid exposure could be reduced to treat relapses of nephrotic syndrome, this would reduce the toxicity of prednisolone and thereby decrease the side effects and long-term complications associated with corticosteroid therapy in children with relapsing nephrotic syndrome.

Trial status

The study started recruitment in December 2016 and is currently recruiting.

Competing interests

None declared

Funding statement

This work was supported by a Senior Postdoc Grant to MFS from the Dutch Kidney Foundation, project number 15OKG16.

Authors' contributions

MFS, principal investigator of the RESTERN study, initiated the project and drafted the protocol. AMS drafted this manuscript based on the METC approved protocol using the SPIRIT checklist. All authors critically reviewed and revised the manuscript and approved the final manuscript as submitted.

Ethics approval:

This protocol and associated documentation has been approved by the medical ethical committee of Arnhem-Nijmegen and the Dutch Competent Authority (Central Committee on Research Involving Human Subjects, CCMO). The registration number of the RESTERN study is NL8185.091.16, file

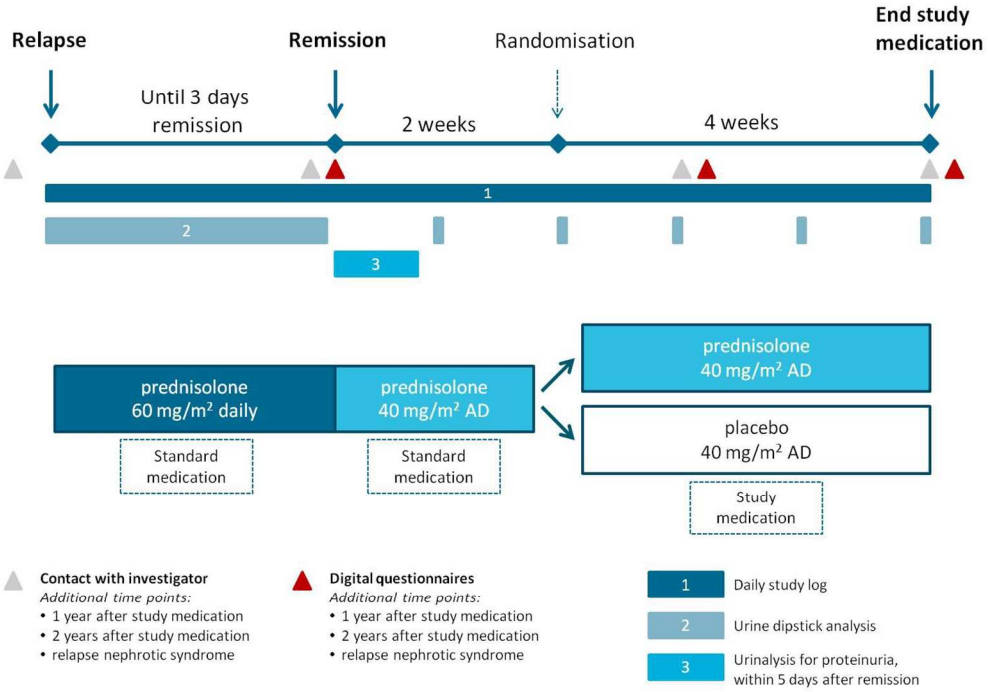
number 2016-2288.

REFERENCES

1. El Bakkali L, Rodrigues Pereira R, Kuik DJ, et al. Nephrotic syndrome in The Netherlands: a population-based cohort study and a review of the literature. *Pediatr Nephrol* 2011;26:1241-6. doi: 10.1007/s00467-011-1851-8 [Published Online First: 1 May 2011]
2. McKinney PA, Feltbower RG, Brocklebank JT, et al. Time trends and ethnic patterns of childhood nephrotic syndrome in Yorkshire, UK. *Pediatr Nephrol* 2001;16:1040-4.
3. Wong W. Idiopathic nephrotic syndrome in New Zealand children, demographic, clinical features, initial management and outcome after twelve-month follow-up: results of a three-year national surveillance study. *J Paediatr Child Health* 2007;43:337-41.
4. Nephrotic syndrome in children: prediction of histopathology from clinical and laboratory characteristics at time of diagnosis. A report of the International Study of Kidney Disease in Children. *Kidney Int* 1978;13:159-65.
5. The primary nephrotic syndrome in children. Identification of patients with minimal change nephrotic syndrome from initial response to prednisone. A report of the International Study of Kidney Disease in Children. *J Pediatr* 1981;98:561-4.
6. Tarshish P, Tobin JN, Bernstein J, et al. Prognostic significance of the early course of minimal change nephrotic syndrome: report of the International Study of Kidney Disease in Children. *J Am Soc Nephrol* 1997;8:769-76.
7. Teeninga N, Kist-van Holthe JE, van Rijswijk N, et al. Extending prednisolone treatment does not reduce relapses in childhood nephrotic syndrome. *J Am Soc Nephrol* 2013;24:149-59.
8. Kyrieleis HA, Lowik MM, Pronk I, et al. Long-term outcome of biopsy-proven, frequently relapsing minimal-change nephrotic syndrome in children. *Clin J Am Soc Nephrol* 2009;4:1593-600. doi: 10.2215/CJN.05691108 [Published Online First: 24 September 2009]
9. Hjorten R, Anwar Z, Reidy KJ. Long-term Outcomes of Childhood Onset Nephrotic Syndrome. *Front Pediatr* 2016;4:53.
10. Ishikura K, Yoshikawa N, Nakazato H, et al. Morbidity in children with frequently relapsing nephrosis: 10-year follow-up of a randomized controlled trial. *Pediatr Nephrol* 2015;30:459-68. doi: 10.1007/s00467-014-2955-8 [Published Online First: 3 October 2014]
11. Skrzypczyk P, Panczyk-Tomaszewska M, Roszkowska-Blaim M, et al. Long-term outcomes in idiopathic nephrotic syndrome: from childhood to adulthood. *Clin Nephrol* 2014;81:166-73.
12. Arneil GC. The nephrotic syndrome. *Pediatr Clin North Am* 1971;18:547-59.
13. Alternate-day versus intermittent prednisone in frequently relapsing nephrotic syndrome. A report of "Arbetsgemeinschaft fur Padiatrische Nephrologie". *Lancet* 1979;1:401-3.
14. Lilien MR, Van de Walle JGJ. Nefrotisch syndroom. In: Van der Heijden AJ, Van Wijk JA, editors. Werkboek Kindernefrologie. 2 ed. Amsterdam: VU University Press 2010:124-131
15. Ehrich JH, Brodehl J. Long versus standard prednisone therapy for initial treatment of idiopathic nephrotic syndrome in children. Arbeitsgemeinschaft fur Padiatrische Nephrologie. *Eur J Pediatr* 1993;152:357-61.
16. Hodson EM, Knight JF, Willis NS, et al. Corticosteroid therapy for nephrotic syndrome in children. *Cochrane Database Sys Rev.* 2005:CD001533.
17. Hoyer PF. New lessons from randomized trials in steroid-sensitive nephrotic syndrome: clear evidence against long steroid therapy. *Kidney Int* 2015;87:17-9.
18. Hahn D, Hodson EM, Willis NS, et al. Corticosteroid therapy for nephrotic syndrome in children. *The Cochrane database of systematic reviews* 2015:CD001533.

19. Larkins N, Kim S, Craig J, et al. Steroid-sensitive nephrotic syndrome: an evidence-based update of immunosuppressive treatment in children. *Arch Dis Child* 2016;101:404-8. doi: 10.1136/archdischild-2015-308924 [Published Online First: 19 August 2015]
20. Yoshikawa N, Nakanishi K, Sako M, et al. A multicenter randomized trial indicates initial prednisolone treatment for childhood nephrotic syndrome for two months is not inferior to six-month treatment. *Kidney Int* 2015;87:225-32. doi: 10.1038/ki.2014.260 [Published Online First: 23 July 2014]
21. Sinha A, Saha A, Kumar M, et al. Extending initial prednisolone treatment in a randomized control trial from 3 to 6 months did not significantly influence the course of illness in children with steroid-sensitive nephrotic syndrome. *Kidney Int* 2015;87:217-24. doi: 10.1038/ki.2014.240 [Published Online First: 16 July 2014]
22. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. KDIGO Clinical Practice Guideline for Glomerulonephritis. *Kidney Int, Suppl.* 2012;2:139–274.
23. https://www.castoredc.com
Date accessed: June 2017
24. Piaggio G, Elbourne DR, Pocock SJ, et al. Reporting of noninferiority and equivalence randomized trials: extension of the CONSORT 2010 statement. *JAMA* 2012;308:2594-604.
25. Schulz KF, Altman DG, Moher D, et al. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;340:c332.
26. http://www.trialregister.nl/trialreg/index.asp
Date accessed: June 2017
27. Jayantha UK. Prolong versus standard steroid therapy for children with relapsing course of nephrotic syndrome [abstract no: P026]. *Pediatr Nephrol* 2004;19:C99.[MEDLINE: CN-00583706]

Figure 1: Intervention schedule and study procedures



Intervention schedule and main procedures
‼ ┼ Abbreviation: AD, alternate days

242x170mm (150 x 150 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2, 14
	2b	All items from the World Health Organization Trial Registration Data Set	All items can be found on www.trialregister.nl Number: NTR5670
Protocol version	3	Date and version identifier	_____
Funding	4	Sources and types of financial, material, and other support	16
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 16-17
	5b	Name and contact information for the trial sponsor	16
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	No role
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	12,13

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3,4
	6b	Explanation for choice of comparators	4
Objectives	7	Specific objectives or hypotheses	4,6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5,6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	7
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	7,9 SAP
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7,8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8,9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9, figure 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	10
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10,11
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10,11
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10,11
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	10,11
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12 + SAP
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12 + SAP
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12 + SAP
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	12,13
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	12,13 + SAP
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	12,13
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	13
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	13

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	14
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	8
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14
	31b	Authorship eligibility guidelines and any intended use of professional writers	
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Study protocol and statistical analysis plan submitted to BMJ open
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Available in Dutch upon request and available on: http://www.restern.nl/informatie-onderzoek/

Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

BMJ Open

REducing STEroids in Relapsing Nephrotic syndrome: the RESTERN study – protocol of a national, double-blind, randomised, placebo controlled, noninferiority intervention study

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REducing STEroids in Relapsing Nephrotic syndrome: the RESTERN study – protocol of a national, double-blind, randomised, placebo controlled, noninferiority intervention study

Schijvens AM[1], Dorresteijn EM[2], Roeleveld CJA[3], ter Heine R[4], van Wijk JAE[5], Bouts AHM[6], Keijzer-Veen MG[7], van de Kar NCAJ[1], van den Heuvel LPWJ[1,8], Schreuder MF[1]

[1]Department of Pediatric Nephrology, Radboudumc Amalia Children's Hospital, Nijmegen, The Netherlands;
[2]Department of Pediatric Nephrology, Erasmus MC - Sophia Children's Hospital, Rotterdam, The Netherlands;
[3]Department for Health Evidence, Radboudumc, Nijmegen, The Netherlands;
[4]Department of Pharmacy, Radboudumc, Nijmegen, The Netherlands;
[5]Department of Pediatric Nephrology, VU University Medical Center, Amsterdam, The Netherlands;
[6]Department of Pediatric Nephrology, Academic Medical Center, Amsterdam, The Netherlands;
[7]Department of Pediatric Nephrology, University Medical Center Utrecht, Utrecht, The Netherlands;
[8]Department of Pediatrics, Department of Growth and Regeneration, University Hospital Leuven, Leuven, Belgium.

Corresponding author:
Anne Merel Schijvens, MD
Department of Pediatric Nephrology
Radboudumc Amalia Children's Hospital
P.O. Box 9101, 6500 HB Nijmegen
The Netherlands, +31 24 36 16783
Anne.Schijvens@radboudumc.nl

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ABSTRACT

Introduction

Oral corticosteroids are the first-line treatment for idiopathic childhood nephrotic syndrome. Most children experience several relapses, needing repeated courses of corticosteroid therapy. This exposes them to side effects and long-term complications. For most patients, long-term prognosis is for complete resolution of the disease over time and maintenance of normal kidney function. Therefore, it is vital to focus on minimizing adverse events of the disease and its therapy. Unfortunately, no randomised controlled trials are available to determine the optimal corticosteroid treatment of an infrequent relapse of nephrotic syndrome. Recent studies show that treatment schedules for the first episode can safely be shortened to two months. The hypothesis of the RESTERN study is that a 4-week reduction of alternate day steroids after inducing remission is effective and safe, reduces steroid exposure by 35% on average, and is therefore preferable.

Methods and analysis

The RESTERN study is a nation-wide, double-blind, randomised, placebo controlled, noninferiority intervention study. Children aged 1-18 years with a relapse of steroid sensitive nephrotic syndrome are eligible for this study. Study subjects (n=144) will be randomly assigned to either current standard therapy in the Netherlands or a reduced prednisolone schedule. The primary outcome of the RESTERN study is the time to first relapse after the final prednisolone dose. The secondary outcomes are the number or relapses, progression to frequent relapsing or steroid dependent nephrotic syndrome and the cumulative dosage of prednisolone during the study period.

Ethics and dissemination

This noninferiority trial will be performed in accordance with the Declaration of Helsinki and has been approved by the medical ethical committee of Arnhem-Nijmegen and the Dutch Competent Authority (Central Committee on Research Involving Human Subjects, CCMO). After completion of this study, results will be published in national and international peer-reviewed scientific journals. Papers will be published according to CCMO guidelines. The final report will be made available to trial participants.

Registration details

Trial registration number NTR5670, EudraCT number 2016-002430-76.

Keywords

Nephrotic syndrome, pediatrics, corticosteroids, randomised clinical trial

Strengths and limitations of this study

- Double-blind, randomised, placebo controlled study
- Nation-wide inclusion
- Large study cohort
- Two common practices in the Netherlands regarding the current treatment of relapsing nephrotic syndrome
- Side effects and toxicity of steroids might jeopardize the double-blind design of the study

INTRODUCTION

Nephrotic syndrome is characterized by the triad of severe proteinuria, hypoalbuminaemia and edema. It is one of the most common glomerular diseases in children with an incidence of 1-7 per 100,000 children per year (Dutch data: 1.52/100,000) and a prevalence of 16 per 100,000 children.[1-3] Most children have minimal change nephrotic syndrome and will have favorable prognosis with complete resolution of the disease over time and maintenance of normal kidney function.[4]

For over 60 years corticosteroids have been the first-line treatment for idiopathic nephrotic syndrome in children as over 80-90% of patients achieve complete remission after prednisolone treatment.[5,6] Yet, over 80% of the patients experience one or more relapses and around 50% suffer from frequent relapses, thereby needing additional courses of corticosteroid therapy.[7] This exposes them to the side effects and long-term complications of corticosteroid therapy, such as growth retardation (8-16%), osteopenia (13-63%), mood disorders, and cataract (6-20%).[8-11] The currently used treatment regimens for a nephrotic syndrome relapse are mostly based on practice guidelines of the International Study of Kidney Disease in Children (ISKDC)[12] and the Arbeitsgemeinschaft für Pädiatrische Nephrologie (APN)[13]. In the Netherlands, the standard treatment schedule consists of 60 mg/m^2 prednisolone daily until complete remission is achieved for 3 days, followed by 40 mg/m^2 prednisolone on alternate days for 4-6 weeks.[14,15]

Several trials have been conducted to study the duration of the initial corticosteroid

treatment regimen, as Hodson et al. suggested that a prolonged period of prednisolone might reduce chances of subsequent relapses.[16] A previous nation-wide study in the Netherlands addressed the issue of duration of corticosteroids for the initial presentation, and showed that the duration had no impact on subsequent relapses.[7] A few recent, well-conducted trials suggest that it may be safe to reduce the duration and thereby cumulative dose of corticosteroid therapy for the initial episode of nephrotic syndrome from six to two or three months.[17-21] With recent studies showing no benefit for longer duration of initial prednisolone treatment, one may conclude that we still don't know the optimal treatment duration of relapses. In addition, as stated in the KDIGO clinical practice guideline glomerulonephritis, "there are no RCTs examining relapse regimens with corticosteroids in infrequent relapsing nephrotic syndrome".[22] With the current evidence against longer steroid therapy for the initial treatment, the time is now to determine whether this holds true for treatment of relapses as well in both children with and without maintenance immunosuppressive therapy.

The aim of the RESTERN study (REducing STEroids in Relapsing Nephrotic syndrome) is to assess the safety and effectiveness of a reduced alternate day steroid schedule for treatment of a nephrotic syndrome relapse in comparison with the current standard therapy.

METHODS AND ANALYSIS

Trial design and setting

The RESTERN study is designed as a nation-wide, double-blind, randomised, placebo controlled, noninferiority intervention study with two treatment arms. The study is performed and coordinated by a single center (Radboudumc Amalia Children's Hospital) where the research team is instituted, with inclusion of patients throughout the Netherlands from all secondary and tertiary hospitals.

Eligibility criteria

Children aged over 1 and less than 18 years with steroid sensitive nephrotic syndrome will be assessed for possible inclusion in the study. A detailed description of the in- and exclusion criteria is shown in Table 1.

Table 1: In- and exclusion criteria

Inclusion criteria
• Age over 1 and less than 18 years
• Steroid sensitive nephrotic syndrome
• At least one episode of nephrotic syndrome in the preceding 24 months that was treated with prednisolone
• The last prednisolone use (at a dose over 10 mg/m^2 on alternate days) for the treatment of a previous episode was at least 4 weeks ago
• Subjects without maintenance immunosuppressive therapy • Subjects with maintenance immunosuppressive therapy ▪ Long-term immunosuppressive therapies: levamisole, ciclosporine, tacrolimus, mycophenolate mofetil (Cellcept®), mycophenolate sodium (Myfortic®), prednisolone max. 4 mg/m^2 on alternate days ▪ Cyclophosphamide (oral of intravenous), at least three months post completion of therapy ▪ A single dose or course of intravenous rituximab, at least three months post completion of therapy
• Signed informed consent from the parent or legal representative and/or the patient, depending on the age of the patient
Exclusion criteria
• Steroid resistant nephrotic syndrome
• Receiving, or within 3 months after receiving, cyclophosphamide or rituximab
• Daily prednisolone maintenance therapy at any dose
• Alternate day prednisolone maintenance therapy at a dose over 4 mg/m^2

• Documented or suspected significant non-compliance
• Pregnancy
• Stimulant drug use
• Comorbidity - Kidney transplant recipient - Any disease that requires the variation in oral prednisolone to be at the discretion of the treating physician(s)
• Concomitant use of moderate and strong CYP3A inducers
• Concomitant use of moderate and strong CYP3A inhibitors, other than cyclosporine

Study objectives

The primary objective of this study is to investigate the effectiveness of a reduced steroid schedule for the treatment of a relapse in children with steroid sensitive nephrotic syndrome. Secondary objectives are:

- To study the influence of maintenance immunosuppressive therapy on the effectiveness of a reduced steroid schedule for the treatment of a relapse in children with steroid sensitive nephrotic syndrome. Maintenance immunosuppressive therapies include levamisole, cyclosporine, tacrolimus, mycophenolate mofetil and mycophenolate sodium, and alternate day prednisolone with a maximum of 4 mg/m^2;

- To investigate the occurrence of relapses, frequency of relapses and progression to steroid dependent and frequent relapsing nephrotic syndrome in children with nephrotic syndrome under the standard treatment regimen;

- To study the influence of maintenance immunosuppressive therapy on the occurrence of subsequent relapses, frequency of subsequent relapses and progression to steroid dependent and frequent relapsing nephrotic syndrome under the standard regimen, and;

- To study the effectiveness of a reduced steroid schedule for the treatment of a relapse and occurrence and frequency of subsequent relapses in children with steroid dependent nephrotic syndrome.

Interventions

Eligible patients will be randomised between standard prednisolone treatment and a reduced treatment schedule. At the start of a relapse, participants are treated according to the current standard therapy, consisting of daily oral prednisolone (60 mg/m^2). After three days of remission, defined as three consecutive days of absent proteinuria based on urine dipstick analysis, standard care dictates that prednisolone is changed to an alternate day dosing of 40 mg/m^2 with a maximum of 40 mg. After two weeks of alternate day prednisolone, participants are randomised between the two treatment arms. The standard treatment group will receive an additional 4 weeks of alternate day oral prednisolone (40 mg/m^2, with a maximum of 40 mg) and the placebo group will receive 4 weeks of alternate day oral placebo.(Figure 1) Prednisolone (5 mg/ml) or placebo will be provided as an oral solution (see paragraph "Investigational medicinal product").

Children will be withdrawn if they are unable to take the study medication and will be treated according to the standard treatment regimen (oral prednisolone 40 mg/m^2 on alternate days). Maintenance immunosuppressive therapy, including levamisole, cyclosporine, tacrolimus, mycophenolate mofetil and mycophenolate sodium, is continued throughout the treatment period. Alternate day prednisolone maintenance therapy with a maximum of 4 mg/m^2, is discontinued during the non-randomised treatment and restarted after randomisation, administered at the same day as the study medication. Antihypertensive agents, antiproteinuric agents, and/or diuretics may be continued at the discretion of the treating physician.

All children will be followed for two years and subsequent nephrotic syndrome relapses will be treated according to the current standard treatment protocol in the Netherlands.

Investigational medicinal product

A prednisolone or placebo solution (5 mg/ml) will be produced compliant with current Good Manufacturing Practice (cGMP) at the department of pharmacy of our institute. The standardized formulation of the oral solution is based on the Dutch Pharmacists Formulary (FNA). The investigational medicinal product is an aqueous solution preserved with methylparaben, buffered at

a pH of 7.1 with a phosphate buffer and contains sorbitol and banana essence to mask the bitter taste of prednisolone sodiumphosphate. For the placebo, prednisolone sodiumphosphate is left out of the product. A pilot palatability study of the investigational medicinal product showed no relevant visual or taste differences of the drug or placebo. Drug dispensing and accountability is performed on individual basis from the central pharmacy.

Outcomes

The primary outcome of the RESTERN study is the time to first relapse. This is defined as the time (in days) from the final prednisolone dose until the first day of treatment of the next relapse.

Secondary outcomes include the following:

1. The number of relapses per patient after the final prednisolone dose, censored at 12 and 24 months of follow-up;

2. Progression to frequent relapsing nephrotic syndrome, defined as four or more relapses in any 12-month period (KDIGO criteria), censored at 24 months of follow-up;

3. Progression to steroid dependent nephrotic syndrome, defined as two consecutive relapses during corticosteroid therapy, or within 14 days of ceasing therapy (KDIGO criteria), censored at 24 months of follow-up;

4. Cumulative dosage of prednisolone (mg/m^2) during study period, censored at 12 and 24 months of follow-up.

Participant timeline (Figure 1)

During the period of daily prednisolone, participants determine the timing of remission by daily urine dipstick analysis. In order to objectively establish remission of nephrotic syndrome, participants are requested to deliver a urine sample to the local hospital within 5 days of attaining remission to confirm the absence of proteinuria. During the two weeks of alternate day prednisolone and the

subsequent 4 weeks of study medication, participants are requested to check their urine for proteinuria at least weekly. In addition, patients are requested to fill out digital questionnaires at different time points. (Figure 1) As shown in Table 2, follow-up information will be collected at 1 and 2 years after randomisation and when a relapse occurs.

Table 2: Study questionnaires

Questionnaire	Information	Time points
Questionnaire 1	General information, medical history, relapse information	At the start of alternate day prednisolone
Questionnaire 2	Information study medication period	One week after initiation of study medication
Questionnaire 3	Information after study medication period	After the final dose of study medication
Questionnaire 4	Information subsequent relapses	At the time of a new relapse
Questionnaire 5	Follow-up 1 year	One year after randomisation
Questionnaire 6	Follow-up 2 years	Two years after randomisation

Sample size

The sample size calculation is based on the noninferiority design and calculated for the primary outcome: time to first relapse after the final prednisolone dose. Based on previous data, average time to relapse in the first year is approximately 185 days with a standard deviation of 120 days.[7] Using the power calculation for a noninferiority trial with a continuous primary outcome, a power of 80% and a noninferiority limit of 50 days, 72 patients per group are required. Using a Cox Proportional Hazard time-to-relapse analysis (survival analysis), similar numbers can be calculated. With an estimated prevalence of nephrotic syndrome of 15 in every 100,000 children, a population most at risk between the ages of 2 and 12 years, about 270 children may be at risk of developing a nephrotic syndrome relapse each year. The necessary inclusion rate is therefore approximately 50%. Subjects will be replaced after withdrawal. Based on withdrawal rates of a previous nephrotic syndrome clinical trial in The Netherlands (Teeninga et al., 2013) a maximum of 23 subjects (=16%) will be replaced. The reason for withdrawal will be recorded in the medical status report and the trial

master file.

Recruitment

Study subjects will be notified about the existence of the RESTERN study via their treating physician, the patient associations and/or the study website (www.restern.nl). Written informed consent for participation will be obtained from the parents or legal representative(s) and/or the patient, depending on the age of the patient.

Randomisation and blinding

Participants will be randomly allocated in a 1:1 ratio to receive either prednisolone or placebo. The randomisation will be performed by the pharmacy of our institute using the data management system Castor Electronic Data Capture[23] with stratification for treatment with immunosuppressive maintenance therapy. Castor uses a variable block algorithm with random blocks of 4, 6 or 8. The randomisation list remains preserved by the pharmacy and will not be accessible to the investigators until the end of the follow-up of the last patient. An unblinding procedure at the hospital pharmacy department will be available at all times. The true group allocation will be unmasked only if necessary and after the database is locked.

Data collection

Participants are requested to maintain a digital study log in which results from dipstick analysis, medication and special remarks are gathered. In addition, participants receive digital questionnaires about their medical history, previous relapses and the current nephrotic syndrome relapse. Moreover, the digital questionnaires include questions about side effects and steroid toxicity at different time points, e.g. during the period of daily prednisolone, alternate day prednisolone and study medication. First, patients are asked if the different side effects were present during the

specific time period. Second, the level of inconvenience is assessed (ranging from not at all inconvenient to very inconvenient). Local pediatricians and pediatric nephrologists will be requested to provide patient information at different time points. Patients randomised who did not take their allocated treatment will be considered as having deviated from the protocol. If a patient or their representative withdraws consent for data collection, only data up to the point of withdrawal will be used in the analysis.

Data management

The study will use the Good Clinical Practice (GCP) compliant, web-based application Castor Electronic Data Capture to record data.[23] Data will be entered in the case report form in Castor by the coordinating investigators at the Radboudumc. The digital questionnaires will automatically be uploaded in the data management system.

Statistical analysis

Statistical analysis will be conducted using IBM SPSS Statistics. A p-value <0.05 will be considered statistically significant. The main analysis will consist of an intention-to-treat analysis. Participants who are lost to follow-up or in whom trial medication is stopped prematurely will be analyzed according to their allocated groups. In addition, as intention-to-treat analysis may increase the risk of type 1 errors in a non-inferiority trial, a per-protocol analysis will also be conducted.[24] Missing baseline and outcome data will not be imputed. When a patient is lost to follow-up or has withdrawn consent, all available data up until withdrawal of consent or loss to follow-up will be used. Discrete variables will be summarized by frequencies and percentages. Continuously distributed variables will be summarized using either mean and standard deviation (SD) for data with normal distribution, or median and interquartile range (IQR) for non-normally distributed data. Further details regarding statistical analysis of the primary and secondary outcomes can be found in the statistical analysis

plan (supplementary file).

Monitoring

As the standard treatment group will receive the current standard therapy for a nephrotic syndrome relapse in the Netherlands, no specific safety surveillance is needed for this group. The placebo arm provides the participants with a reduced prednisolone exposure, which is therefore unlikely to result in any adverse events. However, the main concern in this study is that the reduced treatment schedule may result in an earlier relapse, which is the primary endpoint of the study. An external Data Safety and Monitoring Board (DSMB) will be convened to monitor safety outcomes and to provide the principal investigator with recommendations regarding reconsideration of the trial. The DSMB will consist of two members: a methodologist and a pediatric nephrologist with experience in clinical trials, both independent of the trial. Interim analysis performed by the DSMB, will take place three months after the first 40 participants have received study medication. Aim is to check for a significant difference in relapse rate between the two groups. Further details about the interim analysis can be found in the statistical analysis plan. An independent research coordinator will monitor the study to verify that the rights and well-being of human subjects are protected, the reported trial data are accurate, complete, and verifiable from source documents and the conduct of the trial is in compliance with the currently approved protocol and GCP. The coordinating investigators will report the serious adverse events and will submit an annual safety report to the medical ethical committee and Competent Authority.

ETHICS AND DISSEMINATION

Ethics approval

The RESTERN study has been approved by the medical ethical committee of Arnhem-Nijmegen and the Dutch Competent Authority (Central Committee on Research Involving Human Subjects, CCMO). The registration number of the RESTERN study is NL8185.091.16. The project will be conducted in

line with the declaration of Helsinki. In addition, all researchers will follow the guidelines for Good Clinical Practice and trial outcomes will be reported in line with the Consolidated Standards of Reporting Trials (CONSORT) guidelines.[25] Any substantial amendments or modifications of the protocol will be presented to the medical ethical committee and, when approved, be notified to the Competent Authority compliant with EU regulations.

Consent

Written informed consent for participation will be obtained from the parents or legal representatives and/or the patient, depending on the age of the patient. Patients will be informed that withdrawal from the study is possible at any time at their own discretion without necessarily giving reasons. The 'Code of conduct involving minors' will be used as guideline to respond appropriately to resistance of subjects to study procedures as established by the Paediatric Association Of The Netherlands.

Confidentiality

All patients have their own unique patient identification number as allocated by the hospital administration. Source data will be stored confidentially in the hospital information system under the subject's identification number. Participants will also receive an identification code, all final study data will be kept under this identification number. The investigators safeguard the key to the code. Handling of personal data will comply with the Dutch Personal Data Protection Act. Data will be stored until fifteen years after publication.

Dissemination policy

The trial is registered on the Dutch Trial Registry, trial number NTR5670, prior to the start of inclusion.[26] After completion of this study, results will be published in national and international peer-reviewed scientific journals. Papers will be published according to CCMO guidelines. The final

report will be made available to trial participants.

DISCUSSION

The RESTERN study aims to demonstrate that relapses of nephrotic syndrome in children can be treated effectively and safely by a reduced duration of alternate day prednisolone. Using a nation wide, double-blind, randomised, placebo controlled, noninferiority study, the hypothesis will be tested.

Currently, corticosteroid treatment duration in children with infrequent relapses of steroid sensitive nephrotic syndrome is based on empirical recommendations from the ISKDC and APN. The RESTERN study is the first randomised placebo controlled clinical trial to investigate a reduced corticosteroid schedule for the treatment of relapsing nephrotic syndrome in childhood. So far, most studies have been conducted to investigate the initial treatment schedule. Recently, it has been shown that a reduction in prednisolone duration for the treatment of a first presentation of nephrotic syndrome in children, with or without increased cumulative dosage, is clinically safe and results in similar treatment outcomes, while potentially reducing side effects.[17,18,20,21] For frequent relapsing nephrotic syndrome an abstract from a single randomised controlled trial suggests that children with relapsing steroid sensitive nephrotic syndrome relapse less frequently if treated with tapering doses of prednisolone for seven months compared to the standard treatment of two months. Unfortunately, these results have never been published, which makes it impossible to examine them closely and evaluate for any bias.[18,27]

In this study a treatment duration of 6 weeks alternate day prednisolone after inducing remission for the standard therapy group was chosen as this is the current standard therapy in the Netherlands for the treatment of a nephrotic syndrome relapse. As the KDIGO recommendation of at least 4 weeks alternate day steroid treatment is based on a rather small study [28], the Dutch guidelines traditionally follow the 6 week alternate day steroid schedule described by the Arbeitsgemeinschaft für Paediatrische Nephrologie (APN). However, a potential limitation of this

study could be that some clinicians already reduced the alternate day treatment schedule from 6 to 4 weeks after inducing remission based on the notion of this in the KDIGO guideline.[22] Our choice of 6 weeks alternate day prednisolone may therefore discourage eligible patients to participate in our study as this may increase the prednisolone duration for some patients. The use of different treatment protocols in the Netherlands underlines the need for our randomised controlled trial to determine the optimal dosing regimen for a nephrotic syndrome relapse. In case noninferiority is shown, our results are also transferrable to the KDIGO recommendation of at least four weeks of alternate day steroid treatment. However, in case inferiority is shown, additional research is needed.

The results of the RESTERN study may provide evidence to adapt current recommendations for national and possibly international guidelines to treat children with relapsing nephrotic syndrome. If corticosteroid exposure could be reduced to treat relapses of nephrotic syndrome, this would reduce the toxicity of prednisolone and thereby decrease the side effects and long-term complications associated with corticosteroid therapy in children with relapsing nephrotic syndrome.

Trial status

The study started recruitment in December 2016 and is currently recruiting.

Competing interests

None declared

Funding statement

This work was supported by a Senior Postdoc Grant to MFS from the Dutch Kidney Foundation, project number 15OKG16.

Authors' contributions

MFS, principal investigator of the RESTERN study, initiated the project and drafted the protocol. AMS

drafted this manuscript based on the METC approved protocol using the SPIRIT checklist. All authors critically reviewed and revised the manuscript and approved the final manuscript as submitted.

Ethics approval:

This protocol and associated documentation has been approved by the medical ethical committee of Arnhem-Nijmegen and the Dutch Competent Authority (Central Committee on Research Involving Human Subjects, CCMO). The registration number of the RESTERN study is NL8185.091.16, file number 2016-2288.

REFERENCES

1. El Bakkali L, Rodrigues Pereira R, Kuik DJ, et al. Nephrotic syndrome in The Netherlands: a population-based cohort study and a review of the literature. *Pediatr Nephrol* 2011;26:1241-6. doi: 10.1007/s00467-011-1851-8 [Published Online First: 1 May 2011]
2. McKinney PA, Feltbower RG, Brocklebank JT, et al. Time trends and ethnic patterns of childhood nephrotic syndrome in Yorkshire, UK. *Pediatr Nephrol* 2001;16:1040-4.
3. Wong W. Idiopathic nephrotic syndrome in New Zealand children, demographic, clinical features, initial management and outcome after twelve-month follow-up: results of a three-year national surveillance study. *J Paediatr Child Health* 2007;43:337-41.
4. Nephrotic syndrome in children: prediction of histopathology from clinical and laboratory characteristics at time of diagnosis. A report of the International Study of Kidney Disease in Children. *Kidney Int* 1978;13:159-65.
5. The primary nephrotic syndrome in children. Identification of patients with minimal change nephrotic syndrome from initial response to prednisone. A report of the International Study of Kidney Disease in Children. *J Pediatr* 1981;98:561-4.
6. Tarshish P, Tobin JN, Bernstein J, et al. Prognostic significance of the early course of minimal change nephrotic syndrome: report of the International Study of Kidney Disease in Children. *J Am Soc Nephrol* 1997;8:769-76.
7. Teeninga N, Kist-van Holthe JE, van Rijswijk N, et al. Extending prednisolone treatment does not reduce relapses in childhood nephrotic syndrome. *J Am Soc Nephrol* 2013;24:149-59.
8. Kyrieleis HA, Lowik MM, Pronk I, et al. Long-term outcome of biopsy-proven, frequently relapsing minimal-change nephrotic syndrome in children. *Clin J Am Soc Nephrol* 2009;4:1593-600. doi: 10.2215/CJN.05691108 [Published Online First: 24 September 2009]
9. Hjorten R, Anwar Z, Reidy KJ. Long-term Outcomes of Childhood Onset Nephrotic Syndrome. *Front Pediatr* 2016;4:53.
10. Ishikura K, Yoshikawa N, Nakazato H, et al. Morbidity in children with frequently relapsing nephrosis: 10-year follow-up of a randomized controlled trial. *Pediatr Nephrol* 2015;30:459-68. doi: 10.1007/s00467-014-2955-8 [Published Online First: 3 October 2014]
11. Skrzypczyk P, Panczyk-Tomaszewska M, Roszkowska-Blaim M, et al. Long-term outcomes in idiopathic nephrotic syndrome: from childhood to adulthood. *Clin Nephrol* 2014;81:166-73.
12. Arneil GC. The nephrotic syndrome. *Pediatr Clin North Am* 1971;18:547-59.

13. Alternate-day versus intermittent prednisone in frequently relapsing nephrotic syndrome. A report of "Arbetsgemeinschaft fur Padiatrische Nephrologie". *Lancet* 1979;1:401-3.
14. Lilien MR, Van de Walle JGJ. Nefrotisch syndroom. In: Van der Heijden AJ, Van Wijk JA, editors. Werkboek Kindernefrologie. 2 ed. Amsterdam: VU University Press 2010:124-131
15. Ehrich JH, Brodehl J. Long versus standard prednisone therapy for initial treatment of idiopathic nephrotic syndrome in children. Arbeitsgemeinschaft fur Padiatrische Nephrologie. *Eur J Pediatr* 1993;152:357-61.
16. Hodson EM, Knight JF, Willis NS, et al. Corticosteroid therapy for nephrotic syndrome in children. *Cochrane Database Sys Rev.* 2005:CD001533.
17. Hoyer PF. New lessons from randomized trials in steroid-sensitive nephrotic syndrome: clear evidence against long steroid therapy. *Kidney Int* 2015;87:17-9.
18. Hahn D, Hodson EM, Willis NS, et al. Corticosteroid therapy for nephrotic syndrome in children. *The Cochrane database of systematic reviews* 2015:CD001533.
19. Larkins N, Kim S, Craig J, et al. Steroid-sensitive nephrotic syndrome: an evidence-based update of immunosuppressive treatment in children. *Arch Dis Child* 2016;101:404-8. doi: 10.1136/archdischild-2015-308924 [Published Online First: 19 August 2015]
20. Yoshikawa N, Nakanishi K, Sako M, et al. A multicenter randomized trial indicates initial prednisolone treatment for childhood nephrotic syndrome for two months is not inferior to six-month treatment. *Kidney Int* 2015;87:225-32. doi: 10.1038/ki.2014.260 [Published Online First: 23 July 2014]
21. Sinha A, Saha A, Kumar M, et al. Extending initial prednisolone treatment in a randomized control trial from 3 to 6 months did not significantly influence the course of illness in children with steroid-sensitive nephrotic syndrome. *Kidney Int* 2015;87:217-24. doi: 10.1038/ki.2014.240 [Published Online First: 16 July 2014]
22. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. KDIGO Clinical Practice Guideline for Glomerulonephritis. *Kidney Int, Suppl.* 2012;2:139–274.
23. https://www.castoredc.com
Date accessed: June 2017
24. Piaggio G, Elbourne DR, Pocock SJ, et al. Reporting of noninferiority and equivalence randomized trials: extension of the CONSORT 2010 statement. *JAMA* 2012;308:2594-604.
25. Schulz KF, Altman DG, Moher D, et al. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;340:c332.
26. http://www.trialregister.nl/trialreg/index.asp
Date accessed: June 2017
27. Jayantha UK. Prolong versus standard steroid therapy for children with relapsing course of nephrotic syndrome [abstract no: P026]. *Pediatr Nephrol* 2004;19:C99.[MEDLINE: CN-00583706]
28. Nephrotic syndrome in children: A randomized trial comparing two prednisone regimens in steroid-responsive patients who relapse early. Report of the International Study of Kidney Disease in Children. *J Pediatr* 1979;95:239-243.

Figure 1: Intervention schedule and study procedures

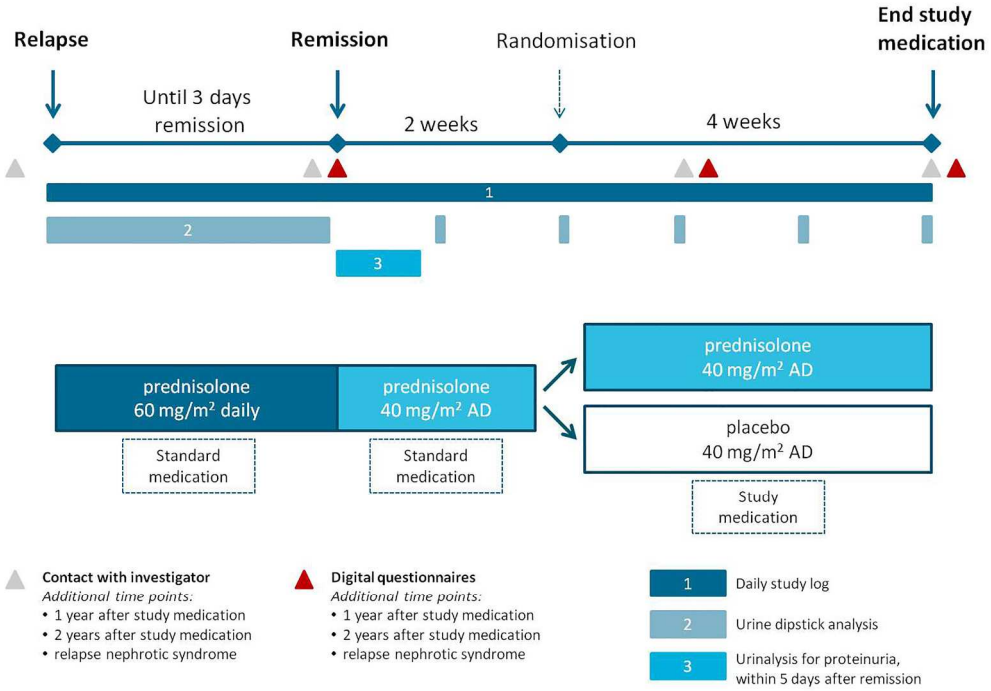


Figure 1: Intervention schedule and study procedures

242x170mm (300 x 300 DPI)

STATISTICAL ANALYSIS PLAN
REducing STEroids in Relapsing Nephrotic syndrome: the RESTERN study

Schijvens AM[1], Dorresteijn EM[2], Roeleveld CJA[3], ter Heine R[4], van Wijk JAE[5], Bouts AHM[6], Keijzer-Veen MG[7], van de Kar NCAJ[1], van den Heuvel LPWJ[1,8], Schreuder MF[1]

[1]Department of Pediatric Nephrology, Radboudumc Amalia Children's Hospital, Nijmegen, The Netherlands;
[2]Department of Pediatric Nephrology, Erasmus MC - Sophia Children's Hospital, Rotterdam, The Netherlands;
[3]Department for Health Evidence, Radboudumc, Nijmegen, The Netherlands;
[4]Department of Pharmacy, Radboudumc, Nijmegen, The Netherlands;
[5]Department of Pediatric Nephrology, VU University Medical Center, Amsterdam, The Netherlands;
[6]Department of Pediatric Nephrology, Academic Medical Center, Amsterdam, The Netherlands;
[7]Department of Pediatric Nephrology, University Medical Center Utrecht, Utrecht, The Netherlands;
[8]Department of Pediatrics, Department of Growth and Regeneration, University Hospital Leuven, Leuven, Belgium.

Corresponding author:
Anne Merel Schijvens, MD
Department of Pediatric Nephrology
Radboudumc Amalia Children's Hospital
P.O. Box 9101, 6500 HB Nijmegen
The Netherlands, +31 24 36 16783
Anne.Schijvens@radboudumc.nl

INTRODUCTION

Background and rationale

The first-line treatment for idiopathic nephrotic syndrome in children is oral corticosteroids.[1] Most children experience several relapses of nephrotic syndrome, needing repeated courses of corticosteroid therapy or even more aggressive treatment with other immunosuppressive drugs. For most children, long-term prognosis is for complete resolution of their disease over time with maintenance of normal kidney function. Therefore, it is vital to focus on minimizing adverse events of the disease and its treatment. The aim of the RESTERN study (REducing STEroids in Relapsing Nephrotic syndrome) is to assess the safety and effectiveness of a reduced alternate day steroid schedule for treatment of a nephrotic syndrome relapse in comparison with the current standard therapy.

Objectives

Primary objective

To study the effectiveness of a reduced corticosteroid schedule for the treatment of a relapse in children with steroid sensitive nephrotic syndrome.

Secondary objectives

- To study the influence of maintenance immunosuppressive therapy on the effectiveness of a reduced steroid schedule for the treatment of a relapse in children with steroid sensitive nephrotic syndrome. Maintenance immunosuppressive therapies include levamisole, cyclosporine, tacrolimus, mycophenolate mofetil and mycophenolate sodium, and alternate day prednisolone with a maximum of 4 mg/m^2;
- To investigate the occurrence of relapses, frequency of relapses and progression to steroid dependent and frequent relapsing nephrotic syndrome in children with nephrotic syndrome under the standard treatment regimen;
- To study the influence of maintenance immunosuppressive therapy on the occurrence of subsequent relapses, frequency of subsequent relapses and progression to steroid dependent and frequent relapsing nephrotic syndrome under the standard regimen, and;
- To study the effectiveness of a reduced steroid schedule for the treatment of a relapse and occurrence and frequency of subsequent relapses in children with steroid dependent nephrotic syndrome.

STUDY METHODS

Trial design

National, single center, double-blind, randomised, placebo controlled, noninferiority intervention study.

Randomisation

After prednisolone 60 mg/m^2 daily in 1 dose until complete remission for 3 days, randomisation (allocation ratio 1:1) between:

- Standard treatment: 6 weeks prednisolone 40 mg/m^2 (max. 40 mg) every other day;

- Study treatment: 2 weeks prednisolone 40 mg/m^2 (max. 40 mg) every other day, then 4 weeks placebo every other day.

Blinding

All researchers involved in the preparation of the analysis plan don't have access to trial data broken down by treatment allocation. Once data quality checks are satisfactory and the database is locked, a blind review will be undertaken to quantify missing data of the entire dataset and allow for any final amendments to the statistical analysis plan. During interim analysis and interpretation, group allocation will be masked using dummy group names (for example, group A, group B). The true group allocation will be unmasked only if necessary and after the database is locked. In addition, due to a difference of 4 weeks between the standard treatment and placebo group regarding timing of final prednisolone dose, time to first relapse and thereby all final statistical analyses can only be determined after unblinding. The randomisation list remains preserved by the hospital trial pharmacy and will not be accessible to the investigators until the end of the follow-up of the last patient. An unblinding procedure at the hospital pharmacy department will be available at all times.

Sample size

From previous studies, we know the incidence of nephrotic syndrome in Dutch children to be 1.52/100,000 children/year.[2] Eighty percent of the pediatric patients develop at least 1 relapse of whom 50% continue towards frequent relapsing nephrotic syndrome. Based on data from previous studies, average time to relapse in the first year is approximately 185 days (standard deviation of 120 days).[3] Using the power calculation for a noninferiority trial with a continuous primary outcome, a power of 80% and a noninferiority limit of 50 days, 72 patients per group are required. Using a Cox Proportional Hazard time-to-relapse analysis (survival analysis)[4], similar numbers can be calculated.

Timing of interim analysis and stopping guidance

Interim analysis will be performed by the Data Safety and Monitoring Board (DSMB), three months after inclusion of the first 40 participants. The study will be terminated in a premature stage if the safety of participants is jeopardized. As the placebo group only receives less active medication (in comparison with the standard treatment group), the occurrence of any serious adverse event is considered highly unlikely. The only risk may be found in the primary outcome of the study, i.e. significant inferiority of the placebo-treatment schedule with regards to time to next nephrotic syndrome relapse.

Timing of final analysis

Final analysis will take place after completion of the 24 months follow-up period of the last study subject.

STATISTICAL PRINCIPLES

Level of confidence intervals and p-values

For this noninferiority trial, the upper bound of the 2-sided 95% confidence interval for the treatment effect has to be below the margin to declare that noninferiority has been shown. P-values <0.05 will be considered statistically significant.

Adherence and protocol deviations

All substantial protocol violations will be listed. Adherence to study treatment (Table 1) will be defined as having consumed 100% of the study medicine, measured by self-report in the medication diary. This will be supported by the participant's returned medication weight/volume.

Table 1: Adherence to study treatment

	Standard treatment (*n* = xxx)	**Placebo (*n* = xxx)**
Self-reported daily dose (mg/m^2/day)		
Week 1		
Week 2		
Week 3		
Week 4		
Participants returning study medication	n/N (%)	n/N (%)
Participants consuming 100% prescribed dose		
Medication diary	n/N (%)	n/N (%)
Returned medication count	n/N (%)	n/N (%)

Analysis populations

The main analysis will consist of an intention-to-treat analysis. Participants who are lost to follow-up or in whom trial medication is stopped prematurely will be analyzed according to their allocated groups. In addition, as intention-to-treat analysis may increase the risk of type 1 errors in a non-inferiority trial, a per-protocol analysis will also be conducted.[5]

STUDY POPULATION

Screening data

Pediatric patients with steroid sensitive nephrotic syndrome are eligible for enrolment.

Eligibility

- Age over 1 and less than 18 years;
- Steroid sensitive nephrotic syndrome with at least 1 episode of nephrotic syndrome in the preceding 24 months.

This will include the following groups:

- Subjects without maintenance immunosuppressive therapy;
- Subjects with maintenance immunosuppressive therapy:
  - Long term immunosuppressive therapies: levamisole, ciclosporine, tacrolimus, mycophenolate mofetil (Cellcept®), mycophenolate sodium (Myfortic®), prednisolone max. 4 mg/m^2 on alternate days
  - Cyclophosphamide (oral of intravenous), at least three months post completion of therapy
  - A single dose or course of intravenous rituximab, at least three months post completion of therapy
- The last prednisolone use (at a dose over 10 mg/m^2 on alternate days) for the treatment of a previous episode was at least 4 weeks ago.

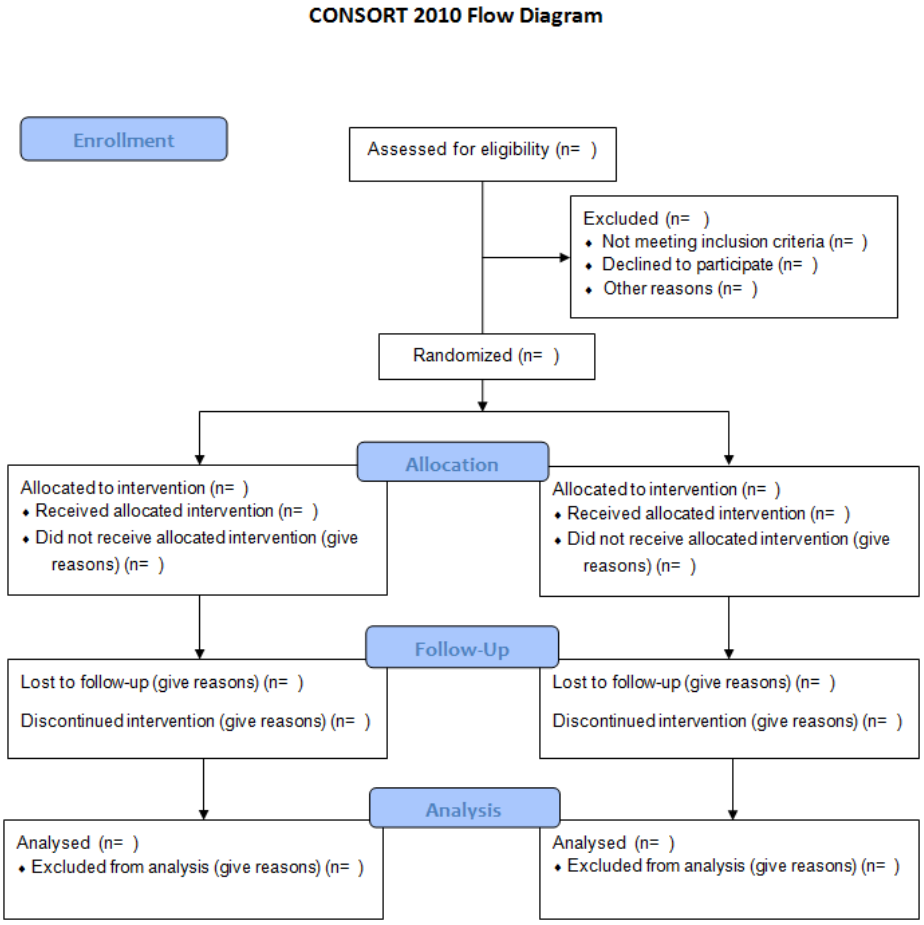
- Subjects experience a relapse nephrotic syndrome, defined as Albustix positive proteinuria (3+ or higher) for three consecutive days or the presence of generalized edema plus 3+ proteinuria on a single occasion.

Exclusion criteria
A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Steroid resistant nephrotic syndrome;
- Receiving, or within 3 months after receiving, cyclophosphamide or rituximab;
- Daily prednisolone maintenance therapy at any dose;
- Alternate day prednisolone maintenance therapy at a dose over 4 mg/m^2;
- Documented or suspected significant non-compliance;
- Pregnancy;
- Stimulant drug use;
- Comorbidity:
  - Kidney transplant recipient
  - Any disease that requires the variation in oral prednisolone to be at the discretion of the treating physician(s)
- Concomitant use of moderate and strong CYP3A inducers;
- Concomitant use of moderate and strond CYP3A inhibitors, other than cyclosporine.

Recruitment
Subjects will be notified via their treating physician, via the patient association and/or the study website about the existence of the RESTERN study. Subjects will be recruited by the research team at the Radboudumc. The trial profile and inclusion will be shown in a Consolidated Standards of Reporting Trials (CONSORT) flow diagram (Figure 1), including the total number of randomised patients and per treatment group the numbers receiving allocated treatment, withdrawing consent, and lost to follow up.

Figure 1: CONSORT flow diagram



Withdrawal/follow-up

Patients randomised who did not take their allocated treatment will be considered as having deviated from the protocol. Their data will be included in both the intention-to-treat and per- protocol analyses. If a patient or their representative withdraws consent for data collection, only data up to the point of withdrawal will be used in the analysis.

Baseline patient characteristics

Discrete variables will be demonstrated by frequencies and percentages. Continuously distributed variables will be demonstrated using either mean ± standard deviation for data with normal distribution, or median and interquartile range for non-normally distributed data.

Table 2: Participant baseline characteristics

	Standard treatment (*n* = xxx)	**Placebo (*n* = xxx)**
Participant characteristics		
Male, n (%)	n/N (%)	n/N (%)
Age, years; median (IQR)	xx.x (xx.x to xx.x), n	xx.x (xx.x to xx.x), n
Age at onset, years; median (IQR)	xx.x (xx.x to xx.x), n	xx.x (xx.x to xx.x), n
Descent, n (%)	n/N (%)	n/N (%)

- Caucasian - Asian - African - Other, specify		
Maintenance therapy, n (%) - Levamisole - Cyclosporine - Tacrolimus - Mycophenolate mofetil - Mycophenolate sodium - Prednisolone	n/N (%)	n/N (%)
Total number of relapses prior to study participation	n/N (%)	n/N (%)
Number of relapses in preceding 24 months	n/N (%)	n/N (%)

ANALYSIS

Outcome definitions

Primary outcome

Time to first relapse

- Definition: time to first relapse (=first day of treatment of the next relapse) after the final prednisolone dose. The final prednisolone dose represents the beginning of study medication for the placebo group and the end of study medication for the prednisolone group.
- Timing: censored at 12 and 24 months
- Measurement value: days

Secondary outcomes

1. Number of relapses
   - Definition: number of relapses per patient after the final prednisolone dose
   - Timing: censored at 12 and 24 months
   - Measurement value: number of patients (%)

2. Progression to frequent relapsing nephrotic syndrome
   - Definition (according to KDIGO criteria): four or more relapses in any 12-month period
   - Timing: censored at 24 months
   - Measurement value: number of patients (%)

3. Progression to steroid dependent nephrotic syndrome
   - Definition (according to KDIGO criteria): two consecutive relapses during corticosteroid therapy, or within 14 days of ceasing therapy
   - Timing: censored at 24 months
   - Measurement value: number of patients (%)

4. Cumulative dosage of prednisolone
   - Definition: cumulative dosage of prednisolone during study period after the final prednisolone dose

- Timing: censored at 12 and 24 months
- Measurement value: mg/m^2

Analysis methods

Primary endpoint

Time to first relapse after the final prednisolone dose

- As normal distribution is not assumed, the median time to relapse will be compared between the groups using a Mann-Whitney test;
- In case patients did not experience any relapse after 24 months or patients are lost to follow up before they experienced a relapse, incidence rates or person-time rates will be used to compare the groups;
- If a normal distribution is shown in the Shapiro-Wilk W test, a *t* test will be used;
- The percentages of study subjects with a relapse at 12 and 24 months will be compared between the groups;
- The cumulative probability on the absence of a relapse will be estimated by survival analysis, according to the Kaplan-Meier method. Log-rank tests are used for the comparison between the standard treatment group and placebo group;
- To test for the influence of factors, such as the use of maintenance immunosuppressive therapy, logistic regression analysis for nephrotic syndrome relapses with covariate analysis will be performed;
- Within each subject time to relapse after study medication will be compared to time to relapse before entering the study using a paired sample *t* test. This test will exclusively be performed in patients without changes in maintenance therapy.

Secondary endpoints

Number of relapses after the final prednisolone dose

- Follow-up will be categorized into three periods (period 1, 0-12 months, period 2, 12-24 months, period 3, 0-24 months) and within each period, the number of relapses is counted;
- Poisson regression will be used to evaluate relapse rates in relation to treatment, maintenance immunosuppressive treatment, sex, age and period.

Development of frequent relapsing nephrotic syndrome (according to KDIGO criteria)

- This categorical outcome will be analyzed with either the Pearson chi-squared or Fisher exact test.

Development of steroid dependent nephrotic syndrome (according to KDIGO criteria)

- This categorical outcome will be analyzed with either the Pearson chi-squared or Fisher exact test.

Cumulative dosage of prednisolone during study period

- Depending on the distribution of the data, this will be analyzed with either the *t* test or the Mann-Whitney test.

Missing data

Missing baseline and outcome data will not be imputed. We will state which data are missing and calculate frequencies using the total number of patients with available data. When a patient is lost to follow-up or has withdrawn consent, we will use all available data up until

withdrawal of consent or loss to follow-up.

Interim analysis

The total inclusion of 144 patients is expected to be finalized in 1.5 years, thereby the DSMB meeting will take place approximately 8 months after the start of inclusion. The mean follow-up period of the 40 patients at that time will be 5.5 (range 3-8) months. Previous literature shows a cumulative incidence rate of a first relapse of 30% after 5.5 months.[3] As the placebo group will receive approximately 35% less prednisolone during the study period, we based the power calculation on a difference of maximum 1/3rd earlier until the first relapse after study medication. Therefore we would like to advise the DSMB to check whether the patients with a relapse are in group A or B (dummy groups) if over 8 patients have experienced a relapse at interim analysis. Aim is then to check for a significant difference in relapse rate between the two groups. If there seems to be a significant difference between the two groups and the percentage of patients with a relapse in either one or both groups exceeds 40% than they might consider to unblind the groups.

Harms

Information on adverse events will be collected by means of reported adverse events in the questionnaires and spontaneous reports from patients and caregivers. The number of adverse events, serious adverse events and suspected unexpected serious adverse reaction will be compared between the two arms using a chi-squared test (or Fisher's exact test), with risk ratios and 95% confidence intervals when these are computable. For all continuous variables either means with standard deviation or medians with interquartile range will be calculated where appropriate and testing for difference will be performed with either the *t* test or Mann-Whitney test where appropriate.

STATISTICAL SOFTWARE

All analyses will be performed with IBM SPSS Statistics.

REFERENCES

1. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. KDIGO Clinical Practice Guideline for Glomerulonephritis. *Kidney Int, Suppl.* 2012;2:139–274.
2. El Bakkali L, Rodrigues Pereira R, Kuik DJ, et al. Nephrotic syndrome in The Netherlands: a population-based cohort study and a review of the literature. *Pediatr Nephrol* 2011;26:1241-6. doi: 10.1007/s00467-011-1851-8 [Published Online First: 1 May 2011]
3. Teeninga N, Kist-van Holthe JE, van Rijswijk N, et al. Extending prednisolone treatment does not reduce relapses in childhood nephrotic syndrome. *J Am Soc Nephrol* 2013;24:149-59.
4. Chow S, Shao J, Wang H. Sample size calculations in clinical research. In: Chapman & Hall/CRC Biostatistics Series. 2 ed. 2008;177.
5. Piaggio G, Elbourne DR, Pocock SJ, et al. Reporting of noninferiority and equivalence randomized trials: extension of the CONSORT 2010 statement. *JAMA* 2012;308:2594-604.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2, 14
	2b	All items from the World Health Organization Trial Registration Data Set	All items can be found on www.trialregister.nl Number: NTR5670
Protocol version	3	Date and version identifier	_____
Funding	4	Sources and types of financial, material, and other support	16
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 16-17
	5b	Name and contact information for the trial sponsor	16
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	No role
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	12,13

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3,4
	6b	Explanation for choice of comparators	4
Objectives	7	Specific objectives or hypotheses	4,6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5,6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	7
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	7,9 SAP
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7,8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8,9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9, figure 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	10
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10,11
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10,11
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10,11
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	10,11
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12 + SAP
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12 + SAP
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12 + SAP
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	12,13
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	12,13 + SAP
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	12,13
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	13
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	13

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	14
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	8
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14
	31b	Authorship eligibility guidelines and any intended use of professional writers	
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Study protocol and statistical analysis plan submitted to BMJ open
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Available in Dutch upon request and available on: http://www.restern.nl/informatie-onderzoek/

Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.